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First synthesis of a selenazepane

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Abstract—The first synthesis of perhydroselenazepane derivatives by the reaction of aryl isoselenocyanates with 5-chlorobutylamine in the presence of triethylamine in DMF as a one-pot procedure is described.

Selenium-containing heterocycles are of great general interest because many of them show attractive chemical properties[1] and pharmaceutical applications.[2] Nowadays, they are recognized as an important class of biologically active compounds.[3] For example, Shamberger[4] and Hatfield[5] widely evidenced the important role of selenium in biology and in human health (cancer chemoprevention, food, and plants).

On the other hand, there are some drawbacks of the syntheses of selenaheterocycles as they often involve the use of toxic selenium reagents, which are difficult to handle and to store. The use of selenoureas and isoselenocyanates, respectively, proved to be among the most efficient methods for the introduction of selenium into heterocycles,[6] as they are conveniently prepared[7] and relatively stable. Some years ago, we started a research program concerning the synthetic potential of isoselenocyanates as building blocks of selenaheterocycles.[8] Recently, we described the synthesis of selenazetidines,[9] selenazolidines,[10] selenazinanes,[10] selenorhodanines,[11] and selenazolidinones[12] from isoselenocyanates by the respective nucleophilic attack of an N, S, and C nucleophile.

To the best of our knowledge, there is no report on the preparation of seven-membered selenium-containing heterocycles, that is, selenazepanes. Only one article has been published recently by a Russian team[13] concerning the synthesis of a selenazepane fused with a pyrimidinone system.

The starting 4-chlorobutylamine, which is commercially not available, was prepared from 4-aminobutan-1-ol. As several attempts to prepare analogous bromo derivatives by treatment with hydrobromic acid[14] were unsuccessful, we used thionyl chloride ($SOCl_2$) in toluene as the reagent,[15] but the usual procedure under reflux did not give the expected product. By using only 1 equiv of $SOCl_2$ in toluene at room temperature, 4-chlorobutylamine hydrochloride (**2**) was obtained in quantitative yield.[16]

The reaction of chloroamine **2** with an aryl isoselenocyanate[7] in DMF in the presence of triethylamine was carried out under stirring at room temperature and led to the corresponding 2-arylimino-1,3-selenazepanes **3a–c** (Scheme 1),[17] which after chromatographic workup were obtained as yellow oils in moderate yield. Some elemental selenium was formed during the reaction, thereby lowering the yield of the product. Triethylamine (2 equiv) was used in this reaction, one equiv to generate the free amine from **2** and a second one to trap the HCl formed in the cyclization. In the case of **3c**, the oily product was dissolved in dichloromethane and crystallized by passing a stream of HCl gas through the solution. The (aryl)(1,3-selenazepan-2-ylidene)amine hydrochloride **3c** was obtained as a colorless solid, and single crystals suitable for an X-ray crystal-structure determination[18] were grown by slow evaporation of the solvent. The molecular structure of **3c**·HCl is shown in Figure 1.[25] The bond lengths of N(3)–C(2) and N(8)–C(2) are quite similar (1.313(3) and 1.337(3) Å, respectively), indicating a distinct delocalization of the N-electron pair and the π-electrons. The Se(1)–C(2) bond is also short (1.902(2) Å) as a result of some conjugation of the lone pair with the π-system. The plane of the aromatic ring is twisted by 52.1(1)° out

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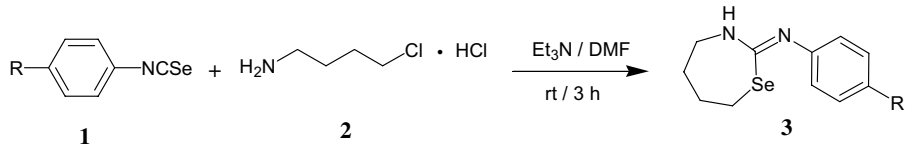

	R	%
a	H	43
b	Me	37
c	Br	48

Scheme 1.

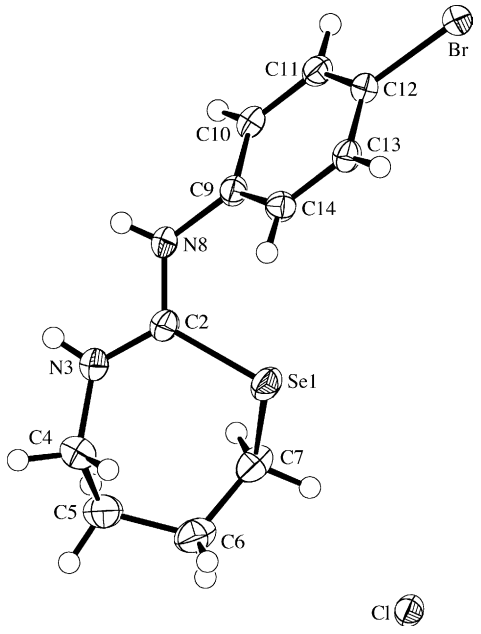

Figure 1. ORTEP plot of the molecular structure of **3c** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability).

of the plane defined by Se(1), C(2), N(3), and N(8). Both NH groups form a hydrogen bond with the same chloride ion and thereby link the cations and anions into ion pairs. The loops thus created can be described with a binary graph set motif[26] of $R_2^1(6)$.

In conclusion, we have described the first synthesis of non-fused 1,3-selenazepane derivatives by a rapid and efficient reaction of isoselenocyanates and 4-chlorobutylamine in moderate yields.

Acknowledgments

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16. *Preparation of 4-chlorobutylamine hydrochloride* (**2**): A solution of 4-aminobutan-1-ol (1 g, 11.22 mmol) and $SOCl_2$ (0.82 mL, 1 equiv) in toluene (15 mL) was stirred at rt for 1 h. Removal of the solvent under reduced pressure afforded crude **2** in quantitative yield as a hygroscopic solid: Mp 145–147 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): 1.76–2.02 (m, 4H, CH_2–CH_2); 3.05–3.12 (m, 2H, $CH_2NH_3^+$); 3.60 (t, $J = 6.2$ Hz, 2H, CH_2Cl); 8.29 (br s, 3H, NH_3^+). ^{13}C NMR (75 MHz, DMSO-d_6): 24.9 (CH_2); 29.2 (CH_2); 39.2 (CH_2N); 43.9 (CH_2Cl). CI-MS (NH_3): 108 (100, $[M-HCl]^+$), 91 (62, $[M-NH_4Cl]^+$).
17. *Typical procedure for the synthesis of selenazepanes* **3**: A 25 mL round-bottom flask equipped with a magnetic stirrer and a condenser was charged with a solution of 4-bromophenyl isoselenocyanate (**1c**, 1.0 mmol) in DMF (20 mL). 4-Chlorobutylamine hydrochloride (**2**, 1.0 mmol) was added, followed by Et_3N (0.28 mL, 2.0 mmol), and the mixture was stirred for 3 h at rt. The mixture was evaporated to dryness under reduced pressure and directly

purified by column chromatography on silica gel with hexane/AcOEt (gradient from 1/0 to 1/1). The yellow oil obtained was then crystallized by passing a stream of HCl gas through a solution of **3c** in dichloromethane. (Phenyl)(1,3-selenazepan-2-ylidene)amine (**3a**): Yield: 43%. Yellow oil. IR (KBr): 3430w (br), 3260–2845m (br), 1606s, 1560s, 1545s, 1475m, 1309m, 1067m, 1011m, 877m, 821m. ^{1}H NMR (300 MHz, $CDCl_3$): 1.69–1.79 (m, 2H, CH_2); 2.18–2.25 (m, 2H, CH_2); 2.84 (t, $J = 7.2$ Hz, 2H, CH_2); 3.51 (t, $J = 7.2$ Hz, 2H, CH_2); 3.75 (br s, 1H, NH); 6.96 (d, $J = 8.2$ Hz, 2H, 2arom. H); 7.05 (t, $J = 8.2$ Hz, 1H, 1arom. H); 7.26 (t, $J = 8.2$ Hz, 2H, 2arom. H). ^{13}C NMR (75 MHz, $CDCl_3$): 24.9 (CH_2); 29.9 (CH_2); 30.3 (CH_2); 46.2 (CH_2); 121.3 (1arom. C); 122.9 (2arom. CH); 128.7 (2arom. CH); 131.0 (1arom. C); 167.3 (N_2CSe). CI-MS (*i*-butane): 122 (100), 195 (93), 251 (21), 252 (19), 253 (44), 254 (17), 255 (72, $[M+1]^+$), 256 (11), 257 (13). Anal. Calcd for $C_{11}H_{14}N_2Se$ (254.03): C 52.18, H 5.57, N 11.06. Found: C 52.01, H 5.63, N 11.00. (1,3-Selenazepan-2-ylidene)(*p*-tolyl)amine (**3b**): Yield: 37%. Yellow oil. IR (KBr): 3428w (br), 3245–2850m (br), 1602s, 1554s, 1549s, 1467m, 1314m, 1066m, 1009m, 867m, 819m. ^{1}H NMR (300 MHz, DMSO-d_6): 1.80–1.85 (m, 2H, CH_2); 2.28 (s, 3H, CH_3); 2.32–2.40 (m, 2H, CH_2); 3.40 (t, $J = 7.2$ Hz, 2H, CH_2); 3.63 (br s, 1H, NH); 3.82 (t, $J = 7.2$ Hz, 2H, CH_2); 6.88, 7.09 (AA′BB′, $J = 8.1$ Hz, 4arom. H). ^{13}C NMR (75 MHz, DMSO-d_6): 20.8 (CH_3), 25.4 (CH_2); 27.8 (CH_2); 27.9 (CH_2); 46.4 (CH_2); 119.4 (1arom. C); 121.1 (2arom. CH); 129.6 (2arom. CH); 133.4 (1arom. C); 168.2 (N_2CSe). CI-MS (*i*-butane): 263 (5), 264 (8), 265 (28), 266 (31), 267 (62), 268 (34), 269 (100, $[M+1]^+$), 270 (19), 271 (18). Anal. Calcd for $C_{12}H_{16}N_2Se$ (268.05): C 53.93, H 3.83, N 7.60. Found: C 54.12, H 5.99, N 10.55.

(4-Bromophenyl)(1,3-selenazepan-2-ylidene)amine hydrochloride (**3c**·HCl): Yield: 48%. Colorless crystals. Mp 170–172 °C (CH_2Cl_2). IR (KBr): 3430w (br), 3206–2750s (br), 1604s, 1579s, 1549s, 1487m, 1328m, 1069m, 1008m, 837m, 821m. ^{1}H NMR (300 MHz, DMSO-d_6): 1.81–1.87 (m, 2H, CH_2); 2.30–2.38 (m, 2H, CH_2); 3.38 (t, $J = 7.2$ Hz, 2H, CH_2); 3.61 (br s, 1H, NH); 3.78 (t, $J = 7.2$ Hz, 2H, CH_2); 7.51, 7.84 (AA′BB′, $J = 8.2$ Hz, 4arom. H). ^{13}C NMR (75 MHz, DMSO-d_6): 26.8 (CH_2); 27.7 (CH_2); 27.8 (CH_2); 46.0 (CH_2); 120.2 (1arom. C); 127.1 (2arom. CH); 132.4 (2arom. CH); 135.7 (1arom. C); 167.6 (N_2CSe). CI-MS (*i*-butane): 328 (3), 329 (19), 330 (20), 331 (56), 332 (30), 333 (100, $[M+1-Cl]^+$), 334 (22), 335 (77), 336 (11), 337 (12). Anal. Calcd for $C_{11}H_{14}N_2SeBrCl$ (367.92): C 35.85, H 3.83, N 7.60. Found: C 35.78, H 3.98, N 7.60.

18. *X-ray crystal-structure determination of* **3c** (Fig. 1).[19] All measurements were performed on a Nonius KappaCCD diffractometer[20] using graphite-monochromated Mo K_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below and a view of the molecule is shown in Figure 1. Data reduction was performed with HKL Denzo and Scalepack.[21] The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method[22] was applied. Equivalent reflections were merged. The structure was solved by direct methods using SIR92,[23] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amine H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. All calculations were performed using the SHELXL97[24] program. Crystal data for **3c**: $C_{11}H_{14}BrClN_2Se$, $M = 368.50$, colorless, tablet, crystal dimensions $0.07 \times 0.22 \times 0.25$ mm, monoclinic, space group $P2_1/c$, $Z = 4$, reflections for cell determination 34297, 2θ range for cell determination 4–60°, $a = 12.6521(3)$ Å, $b = 9.5179(2)$ Å, $c = 12.7661(3)$ Å, $\beta = 119.435(1)°$, $V = 1338.86(6)$ Å^3, $T = 160$ K, $D_X = 1.828$ g cm^{-3}, μ(Mo K_α) = 5.971 mm^{-1}, $2\theta_{(max)} = 60°$, transmission factors (min; max) 0.259; 0.668, total reflections measured 36,227, symmetry independent reflections 3905, reflections with $I > 2\sigma(I)$ 3244, reflections used in refinement 3905, parameters refined 154; $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0317, $wR(F^2)$ [all data] = 0.0814 ($w = [\sigma^2(F_o^2) + (0.0385P)^2 + 0.7741P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.062, secondary extinction coefficient 0.0044(6), final Δ_{max}/σ 0.002, $\Delta\rho$ (max; min) = 0.93; −0.79 e Å^{-3}.
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